AMENDMENT TO THE DRAWINGS

The attached three sheets corresponding to Figures 14B, 14C, and 14D, and are replacement drawings to replace the identical sheets that were mailed on October 12, 2004. Annotated sheets show the addition of SEQ ID NOs, in compliance with 37 CFR 1.821-1.825. The substitute sheets includes an identifier label with the phrase "Replacement Sheet."

Attachment: Replacement Sheets

REMARKS

The Amendments

Claims 1, 13-18, 20 and 21 have been amended. With this submission, claim 31 has been cancelled without prejudice or disclaimer. New claims 32-38 have been added.

Applicant has amended claim 1 so that it is drawn to a chemically modified nucleic acid molecule having the following features: (1) it comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (2) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; (3) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human huntingtin (HD) RNA sequence comprising SEQ ID NO: 3582; (4) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human HD RNA; (5) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications; and (6) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2′-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2′-deoxy-2′-fluoro pyrimidine nucleotides.

Specifically, claim 1 has been amended to recite a chemically modified double stranded short interfering RNA (siRNA) molecule comprising a sense strand and an antisense strand. Support for the amendment can be found in the specification at, *inter alia,* page 8, lines 3-5; page 9, lines 3-5. Claim 1 has also been amended to recite that the antisense strand of the siRNA molecule comprises about 18 to about 27 nucleotides that are complementary to huntingtin (HD) RNA corresponding to SEQ ID NO: 3582, which finds support in the specification at, *inter alia*, page 21, lines 19-23; page 142, lines 5-7; the antisense strand is complementary to the sense strand, which finds support in the specification at, *inter alia* page 11, lines 12-18; the sense strand of the siRNA molecule comprises a portion of the HD RNA nucleotide sequence of about 18 to about 27 nucleotides, which finds support in the specification at, *inter alia* page 21, lines 19-23; and between about 50 percent and about 100 percent of the nucleotide positions in one or both strands of the siRNA molecule are chemically modified and any purine nucleotides present

in the antisense strand are 2'-O-methyl purine nucleotides, which finds support in the specification at, *inter alia* page 13, lines 19-22; Figures 4 and 5 and descriptions thereof. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 3-20, page 12, lines 4-6; pages 55-57 (Table I showing nucleic acid molecules having 50-100% modifications); and page 384, line 7, *see,* NM_002111) and 60/440,129 (*see,* page 7, lines 23-30, page 8, lines 5-11).

Support for amended claim 13 is found in the specification at, *inter alia*, page 17, lines 17-20, and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 3-16) and 60/440,129 (*see,* page 15, lines 14-20 and page 10, lines 10-13).

Support for amended claim 14 is found in the specification at, *inter alia*, page 17, lines 22-25; page 23, lines 4-6; and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/440,129 (*see,* page 22, lines 1-9, and page 10, lines 13-17).

Support for amended claim 15 is found in the specification at, *inter alia*, page 17, lines 17-30; page 23, lines 4-8; and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 3-16, and page 11, lines 1-11) and 60/440,129 (*see,* page 15, lines 14-20, and page 10, lines 10-13).

Support for amended claim 16 is found in the specification at, *inter alia*, page 23, lines 16-19; and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 3-16, and page 11, lines 1-11), and 60/440,129 (*see,* page 16, lines 19-25, and page 21).

Support for amended claim 17 is found in the specification at, *inter alia*, page 23, lines 16-19; and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 40, lines 4-18) and 60/440,129 (*see,* page 20, lines 1-5).

Support for amended claim 18 is found in the specification at, *inter alia*, page 23, lines 12-16; and page 32, lines 9-10. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 3-16, and page 11, lines 1-11) and 60/440,129 (*see,* page 15, lines 4-20, and page 10, lines 10-13).

Support for amended claim 20 is found in the specification at page 23, lines 11-13; and

page 32, lines 7-11. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/440,129 (*see,* page 16, line 27, to page 17, line 13).

Support for amended claim 21 is found in the specification at, *inter alia*, page 19, lines 23-25, and page 23, lines 19-21. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 10, lines 31, to page 11, lines 1-11) and 60/440,129 (*see,* page 24, lines 13-18).

Support for new claim 32 is found in the specification at, *inter alia*, page 14, lines 3-4. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/363,124 (*see,* page 35, lines 29-31; page 27, lines 2-5).

Support for new claim 33 is found in the specification at, *inter alia*, page 19, lines 21-23; and page 23, lines 11-13. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/440,129 (*see,* page 22, lines 25-30, and page 10, lines 13-17).

Support for new claim 34 is found in the specification at, *inter alia*, page 23, lines 22-23. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application Nos. 60/363,124 (*see*, page 9, lines 5-13), and 60/440,129 (*see,* page 13, lines 16-25).

Support for new claim 35 is found in the specification at, *inter alia*, page 25, lines 12-13; page 57, lines 1-3; and page 107, lines 23-26. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/363,124 (*See*, page 18, lines 15-20).

Support for new claim 36 is found in the specification at, *inter alia*, page 17, lines 17-30; page 23, lines 6-8; and page 32, lines 1-18. Support is also found in the priority documents. *See, e.g.*, U.S. Provisional patent application No. 60/440,129 (*see,* page 25, lines 20-25, and page 10, lines 13-17).

Support for new claim 37 is found in the specification at, *inter alia,* page 12, lines 26-30; page 26, lines 6-12; and page 31, lines 4-6. Support is also found in the priority documents. *See, e.g.,* U.S. Provisional patent application No. 60/363,124 (*see,* page 4, lines 9-11, and page 9, lines 5-13).

Support for new claim 38 is found in the specification at, *inter alia,* page 26, lines 6-12. Support is also found in the priority documents. *See, e.g.,* U.S. Provisional patent application No. 60/363,124 (*see,* page 4, lines 9-11; page 5, lines 13-22; and page 9, lines 5-13).

Amendments to the claims are made without prejudice and do not constitute amendments

to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and Applicant respectfully requests their entry.

Priority

The Office asserts that the instant claims are entitled to a priority date of April 11, 2004, which is the filing date of the instant application. The Office declines to accord the instant application the benefit of the earlier priority applications because it alleged that the priority '124 application does not teach a limitation wherein "between about 50 percent and about 100 percent of the nucleotide positions of one or both strands of the siRNA molecule are chemically modified and any purine nucleotides present in the antisense strand are 2'-O-methyl purine nucleotides." Applicant respectfully traverses.

Applicant submits that the claim element reciting "about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methuyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications" is fully supported by U.S. provisional application 60/363,124. For example, pages 10-11 of that application teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, one or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. The specification also teaches that the nucleic acid molecules can have 1-10 phosphorothioate internucleotide linkages in both strands, 1-10 nucleotides of the sense and/or antisense strands chemically modified with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro and/or universal base modified nucleotides, and a terminal cap moiety at the 3'-end, 5'-end, and/or both ends of either or both strands. Based on the size of the molecule (18-27 nucleotides), Applicant submits that one skilled in the art would realize that the specification teaches that about 50-100% of the nucleotides in the antisense and sense strands are chemically modified. Furthermore, Applicant provides numerous examples of specific

chemically modified nucleic acid molecules having about 50-100% chemical modifications in that priority application, especially in Table I, pages 55-57, and Figures 3-10. For example, nucleic acid molecule 28254/28256 has about 50% chemical modifications on both strands. Other examples include 27653 and 27658 (100% chemical modifications); 27655, 27654, 27658, 28254, 27661, 27659, 27660, 27660, and 28244 (50-80% chemical modifications). Table I also includes numerous other examples of nucleic acid molecules having about 50-100% chemical modifications.

The instant application claims priority to and incorporates by reference PCT/US03/05028 in its entirety, which application claims priority to and incorporates by reference 60/363,124 in its entirety. Thus, the instant application properly claims priority to the 60/363,124 application. As discussed above, both the PCT/US03/05028 and 60/363,124 applications fully support the instant claims. Applicant respectfully submits that the instant invention is entitled to a priority date of at least March 11, 2002, the filing date of the '124 application.

Drawing objection

The Office objected to the replacement drawings mailed on October 12, 2004, alleging that the drawings were not identified as either a "Replacement Sheet" or "New Sheet". The Applicant attaches a set of new replacement drawings with the proper identifier. Annotated sheets show the addition of sequence identifier. No new matter has been added to this application as a result of these submissions. Withdrawal of the objection is in order and is respectfully requested.

Rejection under 35 USC § 112, first paragraph

Claim 31 was rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. Claim 31 has been canceled by the present amendment. Applicant respectfully submits that withdrawal of this rejection is in order and is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 13-18, 20, 21 and 31 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Hayden *et al.* (US 2002/0187931 A1) in view of Davidson *et al.* (US 2004/0241854 A1); Tuschl *et al.* (WO 02/44321); Parrish *et al.* (2000, *Molecular Cell*, Vol. 6, p. 1077-1087); Matulic-Adamic et al. (U.S. Patent No. 5,998,203) and Olie et al. (2002,

Biochemica et Biophysica Acta, 1576, p. 101-109). Claim 31 has been canceled, thus rendering the rejection moot as applied to this claim. Applicant respectfully traverses the rejection as it applies to amended claims 1, 13-18, 20 and 21.

The Office relies on Hayden as the primary reference for allegedly teaching the use of antisense targeted to HD gene. However, Hayden *et al.* teach a single stranded antisense molecule targeted to an HD gene. Hayden does not teach or suggest a chemically modified nucleic acid molecule comprising a sense strand and a separate antisense strand. Furthermore, it does not teach a nucleic acid molecule wherein the antisense strand comprises a nucleotide sequence of 18 to 27 nucleotides that is complementary to a human huntingtin (HD) RNA comprising SEQ ID NO:3582.

Davidson is relied on as a secondary reference for allegedly teaching the use of chemically synthesized siRNA molecules targeted against huntingtin gene via RNA interference. However, Davidson does not teach or suggest any chemically modified nucleotides, thus cannot be used to support an obviousness rejection because the instant claims are specifically drawn to a **chemically modified** nucleic acid molecule. Furthermore, Davidson was filed on June 2, 2004, but claims priority to an earlier application filed on August 5, 2002. But as explained above, the instant claims are entitled to a priority date of at least March 11, 2002. Therefore Davidson is non-applicable post-filing art.

Matulic-Adamic is relied on for allegedly teaching a terminal cap moiety at the 5'-end, 3'-end or both ends, including an inverted deoxyabasic moiety. However, Matulic-Adamic teach chemical modification of ribozymes. For the reasons discussed in more details below, ribozyme art is non-analogous art to the claimed invention. At the time of the priority date, although very little is known about the mechanism of action of siRNAs, those of ordinary skill in the art did know that ribozymes function in very different ways from siRNAs, and accordingly could be expected to require different structural features for activity.. Thus the Office should not have relied upon Matulic-Adamic as a basis for an obviousness rejection in this case.

Tuschl is relied on for allegedly teaching chemically modified siRNA duplexes for mediating RNAi of a target gene. However, Tuschl expressly teaches away from highly modified siRNA constructs. Tuschl teaches that extensive substitution with 2'-deoxy or 2'-O-methyl modifications abolishes RNAi activity. In a section tellingly entitled, "The siRNA User Guide," Tuschl expressly teaches away from highly modified siRNA constructs:

"The siRNA User Guide"

> Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and **must** be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 2'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes. **More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi**, probably by interfering with protein association for siRNAp assembly. (*see*, paragraphs [0178] to [0179]) (emphasis added).

Tuschl thus expressly states that more than a few end modifications should be avoided. Thus the highly modified constructs now being claimed were not made at the time of the priority date with a reasonable expectation of success.

Parrish is relied on for its alleged teachings concerning chemically modified double stranded siRNA molecules having 2-deoxy-2'-fluoro pyrimidne modifications in the sense or antisense strand. Contrary to the Office's position, Parrish does not teach or suggest short, chemically modified, double-stranded nucleic acid molecules comprising 2'-deoxy-2'-fluoro pyrimidine modifications. Instead, Parrish teaches long dsRNA molecules. All of the 2'-deoxy-2'-fluoro modifications taught by Parrish were introduced by enzymatic incorporation of 2'-deoxy-2'-fluoro uridine nucleotides into long double stranded RNA molecules (>700 nt), and **not** selective synthetic incorporation of 2'-deoxy-2'-fluoro uridine *and* 2'-deoxy-2'-fluoro cytidine nucleotides (collectively 2'-deoxy-2'-fluro pyrimidine nucleotides) into short interfering RNA molecules. Furthermore, Parrish fails to teach or suggest an siRNA molecule wherein about 50 to 100% of one or both strands are chemically modified and wherein one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

Finally, Olie is relied on for allegedly teaching chemically modified antisense oligonucleotides with 2'-O-modifications. However, Olie teaches chemical modification of antisense oligonucleotides, and for the reasons discussed in more details below, antisense art is non-analogous to the art in which the presently claimed invention is encompassed. At the time of the priority date, although little is known about the specific mechanism of action of siRNAs, those of ordinary skill in the art did know that the antisense molecules and siRNAs functioned in very different ways, and therefore would have anticipated that different structural features of

nucleic acids would have been required for their activities. Thus, the Office should not have based its obviousness rejection on Olie.

The Office argues that it would have been obvious to one skilled in the art to make an siRNA molecule as allegedly taught by Hayden to target a gene encoded by HD, as allegedly taught by Davidson and would have further been obvious to make a chemically modified siRNA as taught by Tuschl and Matulic-Adamic. The Office argues that one would have been motivated to make such a molecule because Hayden teaches that antisense oligonucleotides can be modified to exhibit desirable properties. The Office further argues that one would have been motivated to place modifications in various locations and vary percentages because Tuschl allegedly teaches testing of siRNA duplexes to optimize performances, and that Olie allegedly teaches stepwise experimentation with oligonucleotides to find the optimal configuration. The Office also argues that each of Tuschl, Parrish, and Matulic-Adamic allegedly taught extensive chemical modification of double stranded nucleic acid molecules and successful inhibition of target gene expression, and that each of the instantly recited chemical modifications were known in the art to be incorporated into siRNAs, long dsRNAs, and ribozymes. The Office finally argues that one skilled in the art would also have a reasonable expectation of success in modifying between 50 and about 100% of the nucleotide positions in one or both strands and arriving at the claimed invention because chemical modifications of oligonucleotides were known in the art at the time of filing and one would expect that such modifications would benefit siRNA because they were shown to modify antisense oligonucleotides, ribozymes, long dsRNA or siRNA duplexes.

Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

None of these references, alone or in combination, render obvious the presently claimed nucleic acid molecules because the cited references do not teach or suggest all of the claim elements. Hayden does not teach siRNA targeted to HD RNA, much less HD RNA comprising SEQ ID NO: 3582. It also does not teach chemically modified siRNA. Matulic-Adamic,

Parrish, and Olie also fail to teach chemically modified siRNA and provide no teaching or motivation to target HD. They also do not teach siRNA, nor do they teach chemical modification of siRNA. Tuschl teaches away from extensive chemical modification of siRNA constructs to the extent as presently claimed. Davidson is not prior art to the instant application.

Thus, none of these references, either alone or in combination, teach a nucleic acid molecule having all the recited elements. In particular, none of the references, either alone or in combination, teach a nucleic acid molecule having the following features: (1) comprising a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; (2) each strand of the nucleic acid molecule being independently 18 to 27 nucleotides in length; (3) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule being complementary to a human huntingtin (HD) RNA sequence comprising SEQ ID NO: 3582; (4) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid molecule being complementary to the antisense strand and comprising an 18 to 27 nucleotide sequence of the human HD RNA; (5) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the antisense strand being chemically modified with modifications independently selected from the group consisting of 2′-O-methyl, 2′-deoxy-2′-fluoro, 2′-deoxy, phosphorothioate and deoxyabasic modifications; and (6) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule being 2′-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule being 2′-deoxy-2′-fluoro pyrimidine nucleotides.

Despite the lack of teaching in the cited references, the Office suggests that it would have been obvious to make double stranded nucleic acid molecules having chemical modifications with a reasonable expectation of success because chemical modification of oligonucleotides, adding stability and specificity to the oligonucleotides, were known in the art and would be expected to benefit siRNA because they had been shown to benefit antisense.

However, Applicant submits that the antisense art and the ribozyme art are not analogous to the siRNA technology, which encompasses the presently claimed invention, and should not be the basis for an obviousness rejection. Any reference or general knowledge cited to demonstrate obviousness must be analogous art. The reference must either be in the field of Applicants' endeavor or, if not, then be reasonably pertinent to the particular problem with which the

inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992).

Specifically, antisense art and ribozyme art are not reasonably pertinent to chemically modified siRNA molecules that target HD RNA. Initially, there are dramatic distinctions between antisense molecules and siRNAs. Antisense molecules are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in a duplex form. It is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Moreover, antisense molecules will tolerate substantial 5' and 3' terminal modifications; in contrast the activities of siRNAs are almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. The activity of an antisense molecule is destroyed by modifications that alter the DNA-like structure at the core of molecule. It was not clear in 2001 whether the siRNA duplex would need to maintain an RNA-like structure for interference activity, or whether other structures would be permitted.

Likewise, ribozymes fall within a non-analogous art. Ribozymes are substantially single-stranded prior to interacting with their target, while siRNA is almost completely in duplex form. It is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Additionally, ribozymes will tolerate substantial 5' and 3' terminal modifications. In contrast, the activity of siRNA molecules is almost completely abolished by attaching modifications to the 5' end of the antisense strand of the siRNA. Also, unlike siRNA molecules, ribozymes must form a complex RNA secondary structure before becoming active.

At the priority date of the present application, while little was known about siRNAs, those of ordinary skill in the art did understand that siRNAs function in a very different way from ribozymes and/or antisense nucleotides. Because of this difference in mechanisms, those of ordinary skill in the art would have anticipated that different structural features would be required for activities in siRNA versus ribozymes and/or antisense nucleotides. Accordingly, they had no basis of predicting the effect of various types and positions of chemical modifications on the activity of a double stranded nucleic acid molecule as claimed herein, let alone the expectation of success.

For the reasons discussed above, the cited references, alone or in combination, do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid

molecules. Accordingly, withdrawal of the 35 USC §103(a) rejection of the claims based on Hayden, Davidson, Tuschl, Parrish, Matulic-Adamic and Olie is in order and is respectfully requested.

Obviousness-Type Double Patenting Rejection

Claims 1, 13-18, 20, 21 and 31 were provisionally rejected on the ground of non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 3, 13-21, 31 and 32 of copending application 10/783,128. Since the rejection is provisional and neither case has been allowed, Applicant requests that the Examiner hold this rejection in abeyance until either application has been allowed.

Conclusion

In view of the foregoing amendments and remarks, Applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Dated: July 30, 2007

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